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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,508	11/30/2006	Anthony John Freemont	69494-4	6795

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EXAMINER
SGAGIAS, MAGDALENE K

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
12/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,508	FREEMONT ET AL.	
	Examiner	Art Unit	
	MAGDALENE K. SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *1-22 and 24-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 August 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/10/06;5/29/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-37 are pending.

Applicant's election without traverse of group V, claim 23 in the reply filed on 9/3/08 is acknowledged.

Claims 1-22, 24-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9/3/08.

Applicants election of the following species for each of the five items: (1) bone marrow in connection with claim 6; (2) the application of load (i.e., step 8(c)) in connection with claim 8; (3) gels in connection with claim 20; (4) TGF□ in connection with claim 28; and (5) genes encoding inhibitors of cytokines in connection with claim 15 is acknowledged. Claim 23 reads on this species election, and is generic with respect to each is acknowledged.

Claim 23 is under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is directed to a method for causing mesenchymal stromal stem cells to differentiate towards IVD cells comprising exposing cultured mesenchymal stromal stem cells to increasing pressures of up to 30 psi (2.1MPa).

The specification teaches Mesenchymal stromal stem cells (MSSCs) were harvested from iliac crest bone marrow aspirates [0095]. Preliminary data shows that degenerate NP cells appear to be hypersensitive to loading at pressures as low as 1 psi (0.0069 Mpa-the minimum load on the intervertebral disc is 0.3 Mpa) [0105]. The specification teaches cellular responses are dependent on cell type and the frequency and amount of load applied [0105]. For instance significant differences were observed in gene expression of degenerate NP cells loaded at 5 psi (0.0345 MPa) and at 7 psi (0.0483 MPa) [0105]. Culture of MSSC cells in alginate cultures under compressive load resulted in equivalent proteoglycan production to NP cells cultured under the same conditions, with an increase in proteoglycan content with time in culture (FIG. 2) [0108]. The specification teaches the inventors found that using more than one differentiation technique could improve differentiation [0126]. For instance, MSSC cells encapsulated in alginate and loaded 3 times a week for 4 hours under a light exercise loading regime (0.8-1.7 MPa, 1 Hz) resulted in a doubling of total proteoglycan content of the alginate construct over 1 and 3 weeks in culture [0126]. Such cells had phenotypes closely resembling natural NP cells. FIG. 14 illustrates proteoglycan production (differentiation markers) from such cells [0126]. However, the specification has failed to provide guidance for differentiation of MSSCs into IVD cells by exposing the MSSCs into increasing pressure only up to 2.1 MPa only as claimed in the instant invention. The specification teaches that identification of intervertebral disk (IVD) cells versus chondrocytes is the matrix production and in order to distinguish chondrocytes from IVD cells the matrix markers are distinguishing IVD cells as compared to chondrocytes are: a) aggrecan gene expression greater than collagen type II; b) proteoglycan versican expression; c)

GAG:hydroxyproline ration greater than 10:1. Applicant's method has not provided any IVD differentiation marker on the MSSCs after the applied pressure alone. Therefore, applicant's method of inducing differentiation of MSSCs into intervertebral disk (IVD) cells raises the issue of whether their asserted IVD cells are actually differentiated IVD cells. The specification fails to teach and/or provide examples as what specific IVD markers are expressed in their cultured IVD cells which will distinguish them from chondrocytes. The specification fails to teach claimed method of differentiating MSSCs into IVD cells as to how to cause MSSCs to differentiate into IVD cells expressing the matrix markers at ratios distinct from chondrocytes since the specification teaches chondrocytes express the matrix markers also at different ratios. At the time of the invention, the art of a causing differentiation of MSSCs into IVD cells was not routine, rather was unpredictable and neither the art of record nor the specification teaches how to practice the claimed invention. An artisan of skill would have required undue experimentation to practice the claimed invention because the method as recited was not routine, the art of differentiating MSSCs to IVD cells was unpredictable and neither the specification nor the art of record teaches how to practice the claimed method, as discussed below:

The specification as filed describes a method for causing MSSCs to differentiate towards IVD cells by exposing the cells to increasing pressure of up to 2.1 MPa. The specification discloses that MSSC cells encapsulated in alginate and loaded under a light exercise loading regime (0.8-1.7 MPa, 1 Hz) resulted in a doubling of total proteoglycan content and such cells had phenotypes closely resembling natural nucleus pulposus (NP) cells as figure 14 illustrates proteoglycan production from such cells. However, the specification fails to provide any guidance for the production of proteoglycan at levels that would distinguish IVD cells from chondrocytes. There is no evidence for the production of IVD differentiation markers at levels specific for IVD cells only. Particularly, since the specification teaches that in order to assess

IVD cell phenotype it needs to be assessed by ensuring that the cells produce a correct matrix (i.e. a IVD matrix rather than a chondrocyte matrix) [0015]. In this respect a skilled person will appreciate that an IVD matrix will be characterized by at least one, and preferably each of, the following: a) aggrecan gene expression should be greater than collagen type II gene expression; b) the proteoglycan versican should be expressed; and c) the GAG: hydroxproline ratio (i.e proteoglycan:collagen ratio) should be greater than 10:1, [0016] [0017] [0018]. At the time of the instant invention the art of MSSC cells differentiation to IVD cells by pressure alone was unpredictable. For example, **Leung et al** (Eur Spine J, 15: (Suppl. 3): S406–S413, 2006) while reviewing the state of the art on MSC differentiation for regeneration of intervertebral disc by MSCs noted that while current therapeutic attempts are aiming to replace or rejuvenate NP cells, the precise phenotype or characteristics of a NP cell is not known (p S410, 1st column, last paragraph). Although they are chondrocyte-like, they do not behave in the same way as chondrocytes (p S410, 1st column, last paragraph). As there are currently no specific markers for NP cells, it is not known whether MSCs can indeed differentiate into NP cells (p S410, 1st column, last paragraph).

As a second issue the claimed invention embraces all species of MSSCs to differentiate to IVD cells. Leung notes many of the small animal models such as rabbits and rats currently used are physiologically different from human IVD both in terms of mechanical loading (emphasis added) and cellular composition (p S410, 1st column bridge to 2nd column). Leung teaches even though larger animal models such as goats or primates could be considered, as their NP structure and mechanical loading are more similar to humans, yet to investigate whether MSCs have themselves differentiated or have induced the differentiation of other cells into true disc cells, the authentic phenotype and molecular signatures of disc cells need to be unambiguously defined (p S410, 2nd column).

These results therefore, question whether a MSSC producing said cell markers could differentiate into an IVD cell as claimed in the instant invention. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for causing MSSCs to differentiate towards IVD cells by exposing MSSCs to increasing pressure, the lack of direction or guidance provided by the specification for causing MSSCs to differentiate towards IVD cells by exposing MSSCs to increasing pressure, the absence of working examples that correlate to causing MSSCs to differentiate towards IVD cells by exposing MSSCs to increasing pressure, the unpredictable state of the art with respect to causing MSSCs to differentiate towards IVD cells by exposing MSSCs to increasing pressure, and the breadth of the claims embraced to any animal species of IVD cells, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAGDALENE K. SGAGIAS whose telephone number is (571)272-3305.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter Paras, Jr./
Supervisory Patent Examiner, Art Unit 1632